

## REMARKS

### Amendments to the Claims

With the present submission, claims 1, 14, 16, 17, 19-21, and 30-31 have been amended. New claims 32-47 have been added. As such, claims 1, 14, 16, 17, 19-21, and 30-47 are under consideration.

Claim 1 has been amended to recite "[a] chemically modified nucleic acid molecule, wherein: a. the nucleic acid molecule comprises a sense strand and a separate antisense strand, each strand having one or more pyrimidine nucleotides and one or more purine nucleotides; b. each strand of said nucleic acid molecule is independently 18 to 27 nucleotides in length; c. an 18 to 27 nucleotide sequence of the antisense strand of said nucleic acid molecule is complementary to a human CHRM3 RNA sequence comprising SEQ ID NO:305; d. an 18 to 27 nucleotide sequence of the sense strand of the nucleic acid molecule is complementary to the antisense strand and comprises an 18 to 27 nucleotide sequence of the human CHRM3 RNA sequence; e. about 50 to 100 percent of the nucleotides in the sense strands and about 50 to 100 percent of the nucleotides in the antisense strand are chemically modified with modifications independently selected from the group consisting of 2'-O-methyl, 2'-deoxy-2'-fluoro, 2'-deoxy, phosphorothioate and deoxyabasic modifications; and f. one or more of the purine nucleotides present in one or both strands of the nucleic acid molecule are 2'-O-methyl purine nucleotides and one or more of the pyrimidine nucleotides present in one or both strands of the nucleic acid molecule are 2'-deoxy-2'-fluoro pyrimidine nucleotides." Support for amended claim 1 can be found in the as-filed specification at, for example, page 10, lines 14-19; page 12, lines 4-8; page 13, lines 1-13 and 17-28; page 14, lines 22-27; page 17, lines 11-30; page 21, lines 16-28; pages 22-23; pages 32-33; page 34, lines 17-27; pages 40-43; Tables I, II, and III; and elsewhere. Support for amended claim 1 can also be found in the priority applications such as U.S. Provisional Application 60/363,124, from which the instant application claims priority, for example, at page 3, lines 15-17; page 5, lines 14-17; page 10, line 3, to page 11, line 25; page 12, lines 4-8; page 18, lines 1-5; page 19, lines 11-14; page 20, lines 13-24; page 21, lines 3-12; page 24, lines 15-22; page 25, lines 17-29; page 29, lines 24-28; page 35, lines 29-30; Tables I & III; and elsewhere.

The term "siRNA" has been replaced by the term "nucleic acid" in each of claims 14, 16, 17, 19-21 and 30-31 to insure proper antecedent basis. Moreover, the term "one or more" in each of claims 14, 19, and 20 has been replaced by the term "1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more," in order to more particularly point out the number of the recited nucleotide in the designated strands. Further amendments have been made to the claims to correct unintended typographic errors, and/or to improve upon grammatical coherence of those claims without affecting their scope. Support for amended claims 14, 16, 17, 19-21 and 30-31 can be found in the as-filed specification as well as in the priority applications, such as U.S. Provisional Application 60/363,124.

Support for amended claim 14 can be found in the as-filed application at, *inter alia*, pages 32-33; and in the priority applications such as U.S. Provisional Application 60/363,124 at, *inter alia*, page 5, lines 14-17; page 10, lines 3-11, and 17-25. Support for amended claim 16 can be found in the as-filed application at, *inter alia*, page 18, lines 6-7; page 23, lines 13-16; page 44, line 30 to page 45, line 2; and in the priority applications such as U.S. Provisional Application 60/363,124 at, *inter alia*, page 10, line 3, to page 11, line 25. Support for amended claim 17 can be found in the as-filed application at, *inter alia*, page 18, lines 6-7; page 23, lines 13-16; page 44, line 30 to page 45, line 2; and in the priority applications such as U.S. Provisional Application 60/363,124 at, *inter alia*, page 8, lines 21-25; page 13, line 18, to page 14, line 9; page 57, lines 8-13 (margin to Figure 9); Table I. Support for amended claim 19 can be found in the as-filed application at, *inter alia*, pages 32-33; and in the priority applications such as U.S. Provisional Application 60/363,124 at, *inter alia*, page 10, line 31, to page 11, line 25. Support for amended claim 20 can be found in the as-filed application at, *inter alia*, pages 32-33; and in the priority applications such as U.S. Provisional Application 60/363,124 at, *inter alia*, page 10, line 31, to page 11, line 25. Support for amended claim 21 can be found in the as-filed application at, *inter alia*, page 23, lines 16-17; page 25, lines 26-28; and in the priority applications such as U.S. Provisional Application 60/363,124 at, *inter alia*, page 9, lines 23-28. Support for amended claim 30 can be found in the as-filed application at, for example, page 20, lines 22-23; page 23, lines 19-20; page 24, lines 18-19. Support for amended claim 30 can also be found in the priority applications such as U.S. Provisional Application 60/363,124 at, for

example, page 8, line 26, to page 9, line 13. Support for amended claim 31 can be found in the as-filed application at, *inter alia*, page 25, lines 9-10; page 57, lines 4-6; and in the priority applications such as U.S. Provisional Application 60/363,124 at, *inter alia*, page 45, line 32, to page 46, line 13.

New claim 32 depends from claim 1, reciting “[t]he nucleic acid molecule of claim 1, wherein 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more of the pyrimidine nucleotides present in the sense strand are 2'-O-methyl pyrimidine nucleotides.” Support for new claim 32 can be found in the as-filed application at, *inter alia*, pages 32-33; and elsewhere. Support for new claim 32 can also be found in the priority applications such as U.S. Provisional Application 60/363,124 at, *inter alia*, page 10, line 2, to page 11, line 25.

New claim 33 depends from claim 1, reciting “[t]he nucleic acid molecule of claim 1, wherein 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more of the pyrimidine nucleotides present in the sense strand are 2'-deoxy-2'-fluoro pyrimidine nucleotides.” Support for new claim 33 can be found in the as-filed application at, *inter alia*, pages 32-33; and elsewhere. Support for new claim 33 can also be found in the priority applications such as U.S. Provisional Application 60/363,124 at, *inter alia*, page 10, lines 1-30.

New claim 34 depends from claim 1, reciting “[t]he nucleic acid molecule of claim 1, wherein 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more of the pyrimidine nucleotides present in the antisense strand are 2'-deoxy-2'-fluoro pyrimidine nucleotides.” Support for new claim 34 can be found in the as-filed application at, *inter alia*, pages 32-33; and in the priority applications such as U.S. Provisional Application 60/363,124 at, *inter alia*, page 10, lines 11-16, 25-30; page 10, line 31, to page 11, line 25.

New claim 35 depends from claim 1, reciting “[t]he nucleic acid molecule of claim 1, wherein said nucleic acid molecule comprises one or more ribonucleotides.” Support for new claim 35 can be found in the as-filed application at, for example, page 71, lines 13-25; and elsewhere. Support for new claim 35 can also be found in the priority applications such as U.S. Provisional Application 60/363,124 at, for example, page 30, lines 17-19, and elsewhere.

New claim 36 likewise depends from claim 1, reciting “[t]he nucleic acid molecule of claim 1, wherein 1, 2, or 3 of the purine nucleotides present in the sense strand are 2'-O-methyl

purine nucleotides." Support for new claim 36 can be found in the as-filed application at, for example, pages 32-33, and elsewhere. Support for new claim 36 can also be found in the priority applications such as U.S. Provisional Application 60/363,124 at, for example, page 10, lines 3-11, 17-25, and elsewhere.

New claim 37 depends from claim 1, reciting "[t]he nucleic acid molecule of claim 1, wherein the antisense strand, sense strand, or both the antisense strand and sense strand include a 3'-overhang of 1-3 nucleotides." New claim 37 finds support in the as-filed application at, for example, page 20, lines 10-14; page 24, lines 1-3; page 43, lines 18-20; and elsewhere. New claim 37 also finds support in the priority applications such as U.S. Provisional Application 60/363,124 at, for example, page 4, lines 9-11, and elsewhere.

New claim 38 depends from claim 37, reciting the nucleic acid molecule of claim 37, wherein the nucleotides of the 3'-overhang are chemically modified as specified. New claim 38 finds support in the as-filed application at, for example, page 19, lines 26-29; page 20, lines 10-16; page 24, lines 1-5; page 25, line 31 to page 26, line 6; page 43, lines 18-23; and elsewhere. New claim 38 also finds support in the priority applications such as U.S. Provisional Application 60/363,124 at, for example, Table I, and elsewhere.

New claim 39 depends from claim 1, reciting the nucleic acid molecule of claim 1, further including "1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more phosphorothioate internucleotide linkages" in one or both strands. New claim 39 finds support in the as-filed application at, for example, pages 32-34; Table III, and elsewhere. New claim 39 also finds support in the priority applications such as U.S. Provisional Application 60/363,124 at, for example, page 9, lines 14-23, 28-30; page 11, lines 6-11; and elsewhere.

New claim 40 depends from claim 1, reciting the nucleic acid molecule of claim 1, further including "1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more 2'-O-methoxyethyl (MOE) nucleotides" in one or both strands. New claim 40 finds support in the as-filed application at, for example, page 44, lines 4-13 and 24-27; and elsewhere.

New claim 41 depends from claim 1, reciting the nucleic acid molecule of claim 1, further including "1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more locked nucleic acid (LNA) nucleotides" in one or both strands. New claim 41 finds support in the as-filed application at, for example, page 40, lines 5-8; page 44, lines 4-13 and 24-26; and elsewhere. New claim 41 also finds support in the priority applications such as U.S. Provisional Application 60/363,124 at, for example, page 37, lines 28-31, and elsewhere.

New claim 42 is independent, reciting "[a] chemically modified nucleic acid molecule comprising a sense strand and a separate antisense strand, wherein: a) each strand of said nucleic acid molecule is independently 18 to 27 nucleotides in length; b) an 18 to 27 nucleotide sequence of the antisense strand of said nucleic acid molecule is complementary to a human CHRM3 RNA sequence comprising SEQ ID NO:305; c) an 18 to 27 nucleotide sequence of the sense strand of said nucleic acid molecule is complementary to the antisense strand and comprises an 18 to 27 nucleotide sequence of the human CHRM3 RNA sequence; d) the sense strand includes a terminal cap moiety at the 5'-end, the 3'-end, or both of the 5' and 3' ends; e) one or more of the nucleotides present in the sense strand and one or more of the nucleotides present in the antisense strand are 2'-O-methyl modified nucleotides; and f) one to ten or more of the pyrimidine nucleotides present in the sense strand and one to ten or more of the pyrimidine nucleotides present in the antisense strand are 2'-deoxy-2'-fluoro pyrimidine nucleotides." New claim 42 finds support in the as-filed application at, for example, page 10, lines 14-19; page 12, lines 4-8; page 13, lines 1-13 and 17-28; page 14, lines 22-27; page 17, lines 11-30; page 21, lines 16-28; pages 22-23; pages 32-33; page 34, lines 17-27; pages 40-43; Tables I, II, and III; and elsewhere. New claim 42 also finds support in the priority applications such as U.S. Provisional Application 60/363,124 at, for example, page 3, lines 15-17; page 5, lines 14-17; page 10, line 3, to page 11, line 25; page 12, lines 4-8; page 18, lines 1-5; page 19, lines 11-14; page 20, lines 13-24; page 21, lines 3-12; page 24, lines 15-22; page 25, lines 17-29; page 29, lines 24-28; page 35, lines 29-30; Tables I & III; and elsewhere.

New claim 43 depends from claim 42, reciting a "composition comprising the nucleic acid molecule of claim 42 in a pharmaceutically acceptable carrier or diluent." New claim 43 finds support in the as-filed application at, for example, page 25, lines 9-10; page 57, lines 4-6;

and elsewhere. New claim 43 also finds support in priority applications such as U.S. Provisional Application 60/363,124 at, for example, page 45, line 32, to page 46, line 13, and elsewhere.

New claim 44 is independent, reciting "[a] chemically modified nucleic acid molecule, wherein: a) the nucleic acid molecule comprises a sense strand and a separate antisense strand, each strand having one or more pyrimidine nucleotides and one or more purine nucleotides; b) each strand of the nucleic acid molecule is independently 18 to 27 nucleotides in length; c) an 18 to 27 nucleotide sequence of the antisense strand of the nucleic acid molecule is complementary to a human CHRM3 RNA sequence comprising SEQ ID NO:305; d) an 18 to 27 nucleotide sequence of the sense strand of the nucleic acid molecule is complementary to the antisense strand and comprises an 18 to 27 nucleotide sequence of the human CHRM3 RNA sequence; e) at least 50% of the nucleotides of each strand of said nucleic acid molecule comprise modified nucleotides having a sugar modification selected from the group consisting of 2'-O-methyl, 2'-deoxy-2'-fluoro, 2'-deoxy, and deoxyabasic modifications; f) at least one of said sugar modifications is a 2'-O-methyl modification; and g) each strand of said nucleic acid molecule has no more than 3 consecutive ribonucleotides." New claim 44 finds support in the as-filed application at, for example, page 10, lines 14-19; page 12, lines 4-8; page 13, lines 1-13 and 17-28; page 14, lines 22-27; page 17, lines 11-30; page 21, lines 16-28; pages 22-23; pages 32-33; page 34, lines 17-27; pages 40-43; Tables I, II, and III; and elsewhere. New claim 44 also finds support in the priority applications such as U.S. Provisional Application 60/363,124 at, for example, page 3, lines 15-17; page 5, lines 14-17; page 10, line 3, to page 11, line 25; page 12, lines 4-8; page 18, lines 1-5; page 19, lines 11-14; page 20, lines 13-24; page 21, lines 3-12; page 24, lines 15-22; page 25, lines 17-29; page 29, lines 24-28; page 35, lines 29-30; page 42, lines 4-16; Tables I & III; and elsewhere.

New claim 45 depends from claim 44, reciting a "composition comprising the nucleic acid molecule of claim 44 in a pharmaceutically acceptable carrier or diluent." New claim 45 finds support in the as-filed application at, for example, page 25, lines 9-10; page 57, lines 4-6; and elsewhere. New claim 45 also finds support in the priority applications such as U.S. Provisional Application 60/363,124 at, for example, page 45, line 32, to page 46, line 13, and elsewhere.

New claim 46 recites "[a] method of modulating the expression of human CHRM3 gene in a cell, comprising administering the chemically modified nucleic acid molecule of claim 1 to the cell under conditions suitable for modulating the expression of human CHRM3 gene in the cell." New claim 46 finds support in the as-filed application at, for example, page 49, line 13, to page 50, line 29; page 52, lines 12-23, and elsewhere. New claim 46 also finds support in the priority applications such as U.S. Provisional Application 60/363,124 at, for example, page 15, lines 10-26, and elsewhere.

New claim 47 recites "[a] method of modulating the expression of human CHRM3 gene in a cell, comprising administering the chemically modified nucleic acid molecule of claim 44 to the cell under conditions suitable for modulating the expression of human CHRM3 gene in the cell." New claim 47 finds support in the as-filed application at, for example, page 49, line 13, to page 50, line 29; page 52, lines 12-23, and elsewhere. New claim 47 also finds support in the priority applications such as U.S. Provisional Application 60/363,124 at, for example, page 15, lines 10-26, and elsewhere.

Amendments to the claims are made without prejudice or disclaimer, and do not constitute amendments to overcome any prior art or other statutory rejections. They are fully supported by the specification as filed, as explained above, and thus do not introduce new matter. Additionally, these amendments are not and should not be construed as admissions regarding the patentability of the claimed subject matter. Applicants reserve the right to pursue the subject matter of previously presented claims in this or in any other appropriate patent application. Accordingly, Applicants respectfully request the entry of the amendments presented herein.

### **Priority**

The Office has accorded an effective filing date of February 20, 2003, the filing date of priority application PCT/US03/05028. Alleging that "application '124 does not teach every limitation of the instant claims," the Office declined to accord the earlier, March 11, 2002, priority date, on which the priority application 60/363,124 was filed. *See* Office Action, at page 3. Specifically, the Office alleged that "application '124 does not teach a limitation wherein 'between 50 and 100 percent of the nucleotide positions in one or both strands of the siRNA molecule are chemically modified' and 'the antisense strand of the siRNA molecule comprises

about 5, 6, 7, 8, 9, 10 or more 2'-O-methyl nucleotides,' as instantly recited." *Id.* Applicants respectfully traverse and submit that the instant claims indeed find support in the '124 application, and therefore should be accorded the priority date of at least March 11, 2002, the date on which the '124 application was filed.

As discussed above in the "Amendments to the Claims" section, amended independent claim 1, as well as the newly added independent claims 42 and 44 all find support in the '124 application. Specifically, the claim element drawn to a chemically modified double-stranded nucleic acid molecule finds support at, for example, page 3, lines 15-17; page 32, lines 11-12; page 35, lines 29-30; page 60, line 20; and elsewhere. The claim element drawn to the complementarity between the sense and antisense strands finds support at, for example, page 12, lines 4-7; page 19, lines 11-14; page 20, lines 16-20; page 21, lines 3-6; page 25, lines 17-29; and elsewhere. The claim element drawn to the antisense strand having 18 to 27 nucleotide complementary to the CHRM3 RNA finds support at page 18, lines 1-5; page 12, line 6; page 418, line 8; Table III; and elsewhere.

Specifically addressing the Office's concerns, Applicants submit that the claim element drawn to "about 50 to 100 percent of the nucleotides in the sense strand and about 50 to 100 percent of the nucleotides in the antisense strand are chemically modified with modifications ..." in amended claim 1e., to "at least 50% of the nucleotides of each strand of said nucleic acid molecule comprises modified nucleotides having a sugar modification ..." in new claim 44e), are fully supported by the '124 application. For example, pages 10-11 of that application teaches that the nucleic acid molecule having 1 to 10 phosphorothioate internucleotide linkages in both strands, one or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro and/or universal base modified nucleotides, and a terminal cap moiety at the 3'-end, 5'-end, and/or both ends of either or both strands. The same section of the specification, and especially lines 6-11 of page 11, teaches that the nucleic acid molecule can, for example, have 1 to 10 phosphorothioate internucleotide linkages in either or both strands, 1 to 10 nucleotides of the sense and/or antisense strands being chemically modified to comprise 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro and/or universal base modified nucleotides, and a terminal cap moiety at the 3'-end, 5'-end, and/or both ends of either or both strands. Because the claimed molecules are 18 to 27 nucleotides in length, those skilled in the art can readily deduce that about 50 to 100 percent of the nucleotides in the antisense and

sense strands may be chemically modified according to the '124 application. Furthermore, the '124 application provides numerous examples of chemically modified nucleic acid molecules having about 50 to 100 percent chemical modifications, especially at pages 55-57 of Table I, and in Figures 3-10. For instance, nucleic acid molecule 28254/28256 comprises about 50% chemical modifications on both strands. Other examples include, but are not limited to, 27653 and 27658 (both comprising 100% chemical modifications); 27655, 27654, 28254, 27662, 27659, 27660, 28244 (each comprising about 50 to 80 percent chemical modifications). Accordingly, 60/363,124 provides ample support for the claim elements described above.

As extensively discussed in the "Amendments to the Claims" section of this response above, the dependent claims also find support in, *inter alia*, the '124 priority application. For the sake of brevity, Applicants do not reiterate the support for these claims here.

On the other hand, the Office appeared to take issue with the propriety of the priority claims made in this application. Specifically, the Office appeared to disagree with Applicants' assertion "that the specification of PCT/US03/05028 incorporates by reference the entire specification of application 60/363,124 and that all other applications in the chain of priority incorporate the earlier applications by reference in their entireties," because "the claims are essential subject matter," which allegedly cannot be "incorporated by reference [unless] to a U.S. patent or U.S. patent application publication," and because "application '124 is a provisional application." Office Action, at pages 2-3 (citing MPEP 608.01(p) and 37 C.F.R. 1.57). It is unclear how the limitations imposed on the incorporation-by-reference practice by MPEP 608.01(p) and 37 C.F.R. 1.57 might, if at all, impact Applicants' right to claim priority to the '124 provisional application. Applicants respectfully note that in the same section of the MPEP, and especially under the subsection titled "Review of Applications Which Are Relied on To Establish an Earlier Effective Filing Date," the MPEP unequivocally states that:

[t]he limitations on the material which may be incorporated by reference in U.S. patent applications which are to issue as U.S. patents **do not apply** to applications relied on only to establish an earlier effective filing date under 35 U.S.C. 119 or 35 U.S.C. 120. Neither 35 U.S.C. 119(a) nor 35 U.S.C. 120 places any restrictions or limitations as to how the claimed invention must be disclosed in the earlier application to comply with 35 U.S.C. 112, first paragraph. Accordingly, an application is entitled to rely

upon the filing date of an earlier application, even if the earlier application itself incorporates essential material by reference to another document. *See Ex parte Maziere*, 27 USPQ2d 1705, 1706-07 (Bd. Pat. App. & Inter. 1993).

(*emphasis added*). The same section of the MPEP further states:

As a safeguard against the omission of a portion of a prior application for which priority is claimed under 35 U.S.C. 119(a)-(d) or (f), or for which benefit is claimed under 35 U.S.C. 119(e) or 120, applicant **may include a statement** at the time of filing of the later application incorporating by reference the prior application. ... The inclusion of such an incorporation by reference statement in the later-filed application will permit applicant to include subject matter from the prior application into the later-filed application without the subject matter being considered as new matter.

(*emphasis added*). Therefore, the priority claims made in the instant application are entirely proper, even including the express statement that "[t]hese [priority] applications are hereby incorporated by reference herein in their entireties, including the drawings," as recommended by the MPEP. *See* page 1 of the instant specification. Because the claims finds support in the '124 application, as explained above, they are entitled to the March 11, 2002, priority date, on which the '124 application was filed.

### **Withdrawal of Previous Claim Objections/Rejections**

#### **Claim Objection**

Applicants acknowledge withdrawal of the various claim objections to claims 1, 3, 10-12, 14, 16, 17, 19-21, 30 and 31.

#### **35 U.S.C. § 102(b) Rejections**

Applicants acknowledge the withdrawal of the 35 U.S.C. § 102(b) rejections of claims 1, 3, and 31 as being obviated by the claim amendments and/or arguments filed on January 24, 2007.

## **35 U.S.C. § 103 Rejections**

Applicants acknowledge the withdrawal of the previous 35 U.S.C. § 103(a) rejections of claims 1, 3, 10-12, 14, 16, 17, 19-21, 30, and 31 in view Agrawal as being obviated by the claim amendments and/or arguments filed on January 24, 2007.

### **Double Patenting**

Claims 1, 14, 16, 17, 19-21, 30, and 31 stand rejected provisionally under the judicially created doctrine of obviousness-type double patenting over U.S. Appl. Ser. No. 10/919,866.

Applicants submit that U.S. Appl. Ser. No. 10/919,866 is no longer pending. Accordingly, Applicants respectfully request withdrawal of the provisional obviousness-type double patenting rejection.

### **Rejections of Claims 1, 13-21, and 34 Under 35 U.S.C. § 103(a)**

Claims 1, 14, 16, 17, 19-21, and 30-31 stand rejected under 35 U.S.C. § 103(a) as being allegedly obvious over Nyce (WO 99/13886), in view of Parrish *et al.* (Molecular Cell., Vol. 6, pages 1077-1087, 2000), Elbashir *et al.* (The EMBO Journal, Vol. 20, No. 23, pages 6677-6888, 2001), Pavco *et al.* (U.S. 6,346,398 B1), Hammond *et al.* (Nature, 2001, Vol. 2, pages 110-119), and Caplen *et al.* (Expert Opin. Biol. Ther., 2003, Jul., 3(4), pages 575-586). Applicants respectfully traverse the rejections.

#### ***a. Priority***

Applicants respectfully note that because the instant claims are entitled to the March 11, 2002, priority date, on which U.S. Provisional Application 60/363,124 is filed, the Caplen reference, published in July of 2003, is not proper prior art to the present claims. Accordingly, the instant claims are not obvious.

But even assuming, *arguendo*, that the instant claims are not accorded the earlier filing date of March 11, 2002, despite being entitled to such a date, the instant claims are not *prima facie* obvious in view of the legal standard of obviousness post-KSR, as explained below.

#### ***b. Post-KSR Legal Framework for Obviousness***

Subsequent to the filing of Applicants' last response, the Supreme Court of the United States addressed the legal standards for determining obviousness under 35 U.S.C. § 103 in *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007).

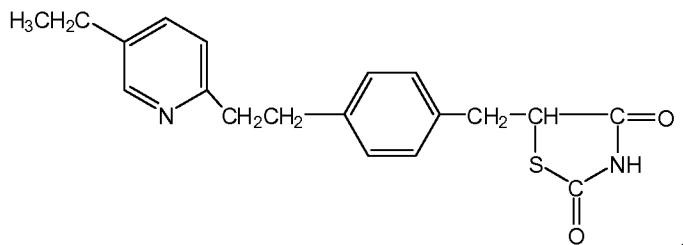
At the outset, reaffirming the objective standard for obviousness set forth in *Graham v. John Deere Co. of Kansas City* (383 U.S. 1, 17-18 (1966)), the *KSR* Court held that the teaching-suggestion-motivation test ("the TSM test") devised by the Federal Circuit Court of Appeals, if not applied in a rigid and mandatory fashion, is consistent with the *Graham* analysis. *KSR*, at 1731. Therefore, arguments and submissions regarding obviousness in Applicants' prior response, which does not follow the TSM test framework rigidly, are still valid post *KSR*.

The *KSR* decision focused on how to determine obviousness when all elements of a claimed invention can be found in the prior art. Recognizing that "inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known," (*KSR*, at 1741), the Supreme Court emphasized three factors: (1) whether there is an "apparent reason to combine the known elements in the fashion claimed by the patent at issue," *id.* at 1740-41; (2) whether, when known elements are combined, there is predictability of yielding the claimed results; and (3) whether the prior art teaches away from modifying known elements in such a way that would lead to the claimed invention.

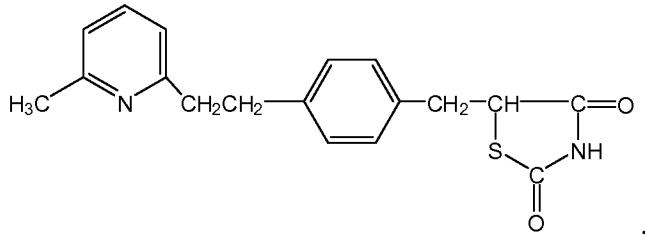
The Court found obviousness in *KSR* because "there is a design need or market pressure to solve a problem [i.e., a reason] and there are **a finite number of identified, predictable** solutions." *See id.*, at 1732 (*emphasis added*). The *KSR* Court emphasized the importance of using teaching-away references to guard against hindsight reconstruction, stating that "[w]hen the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious." *Id.* at 1740 (citing *United States v. Adams*, 383 U.S. 39, 51-52 (1966)). As such, teaching away is significant not only in undermining the reason(s) for making a claimed invention, but also in diminishing the predictability of whether a combination of prior art elements may be successful. As discussed below, the prior art to the instant invention does just that, not only teaching away from making the claimed invention, but also suggesting the lack of predictability.

These factors have subsequently been interpreted by the Federal Circuit on several occasions. For example, applying the framework of *KSR*, the Federal Circuit held it necessary to demonstrate that the prior art provide reasons to make the particular invention and not merely general guidance before finding obviousness in *Pharmastem Therapeutics v. Viacell*, 83 U.S.P.Q.2d 1289, 1350 (Fed. Cir. 2007) (quoting *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988)), and stating that “an invention would not be deemed obvious if all that was suggested was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.”). Therefore, the mere fact that certain approaches can be undertaken does not constitute a legally sufficient reason to combine the known elements in an obviousness inquiry.

*Takeda Chemical Industries v. Alpharma*, 2007 WL1839698, \*15 (Fed. Cir. June 28, 2007), further illustrates the importance of having a finite number of identified, predictable solutions for a finding of obviousness. In *Takeda*, the claim at issue was directed to the compound pioglitazone, wherein an ethyl group is attached to the 5'-position of a pyridyl ring:



The alleged infringer argued that the claim at issue was obvious over the prior art compound b, which includes a pyridyl ring with a methyl group attached at the 6'-position:



The Federal Circuit agreed with the district court's finding of nonobviousness, despite the fact that the claimed compound differs from the alleged prior art compound in merely two aspects: (1) the type of substituent (methyl in compound b vs. ethyl in the claimed compound); and (2)

the location of the substituent (at the 6-position on the pyridyl ring in compound b vs. at the 5-position in the claimed compound). The Federal Circuit found that the prior art would not have first led one of ordinary skill in the art to select compound b as a lead compound for investigation, and then led that person to make two obvious chemical changes: replacing a methyl group with an ethyl group, and "ring-walk" the ethyl group to the 5'-position, despite the fact that compound b was disclosed in a prior art reference. The Federal Circuit called attention to the fact that the reference disclosed hundreds of millions of other compounds in the same family, and exemplified 54 of those compounds, including compound b, but was silent as to which of those compounds would have the desired properties. The Federal Circuit also found it important that another reference also disclosed compound b, but did not identify it as one of the three most favorable compounds, and in fact singled it out as one having prominent undesirable side effects. On these facts, the Federal Circuit approved the district court's finding that a person of ordinary skill in the art would not have selected compound b as a lead compound.

The Federal Circuit then rejected the contention that, under *KSR*, it would have been obvious to pick compound b and modify it as claimed because the prior art compound fell within "the objective reach of the claim," and the evidence demonstrated that using the techniques of homologation and ring-walking would have been "obvious to try." According to the Federal Circuit, this was not a situation when there are a finite number of identified and predictable solutions to a problem. Instead, compound b "exhibited negative properties that would have directed one of ordinary skill in the art away from that compound." *Id.* at \*15. Thus, the Federal Circuit concluded, "this case fails to present the type of situation contemplated by the [*KSR*] Court when it stated that an invention may be deemed obvious if it was 'obvious to try.'" *Id.*

The defendant's reliance on *Pfizer v. Apotex, Inc.*, 480 F.3d 1348 (Fed. Cir. 2007) fared no better. Contrasting *Pfizer*, where obviousness was found because the prior art teaches how to narrow the possibilities of a large family of lead compounds to a group of efficacious ones, the Federal Circuit pointed to the district court's finding of nothing in the prior art to narrow the possibilities of millions of lead compounds to compound b in *Takeda*.

The Federal Circuit went on to state that even if the prior art would have led to the selection of compound b as the lead compound, the obviousness argument failed on a second ground. The Court found nothing in the prior art to suggest making the specific molecular

modification to compound b that would lead to the claimed compounds. The Court also pointed out that studies have confirmed that several other compounds, "and one compound in particular, compound 99, that had no identified problems" in properties "differ significantly from compound b in structure." *Id.* at \*18. The Court concluded that the process of modifying lead compounds was not routine at the time of the invention because of the great number of possible modifications, and because there was no way of predicting which of the modifications might bring about desired properties, especially in view of the fact that similar modifications did not always yield similar changes in properties. Therefore, there is no *prima facie* obviousness even when a general approach to a problem is known, if that general approach yields numerous choices, and the prior art does not help to predict which of those choices would be more efficacious.

*Takeda* also illustrates how a prior art reference teaching away from the claimed invention may further buttress the want of predictability. Specifically, evidence in the prior art that certain modifications produce undesirable properties should be taken as not only leading a skilled artisan away from those particular modifications, but also as suggesting the lack of predictability on how similar modifications may fare. In other words, if the prior art teaches that certain modifications sometimes but not always give rise to the desired properties, there is no way of predicting what other similar modifications may do.

### ***c. The Cited References***

The cited references, alone or in combination, fails to provide a reason or motivation that would have compelled those skilled in the art to chemically modify a double stranded nucleic acid molecule in the specific pattern and to the specific extent as claimed. Nor do the cited references teach those skilled in the art how to predict which of the potentially millions of modified molecules might be efficacious.

The Office alleges that Parish teaches a chemically synthesized siRNA molecule wherein each strand is 26 bp in length and wherein the antisense strand comprises nucleotide sequence that is complementary to a human CHRM3 nucleotide sequence comprising SEQ ID NO: 305 (nucleotides 12-14 of the sense strand are allegedly identical to nucleotides 8-10 of SEQ ID NO;

305)<sup>1</sup>. (see Office action dated July 24, 2006). The Office further alleges that Parrish teaches 2'-deoxy-2'fluoro pyrimidines modifications in the sense or antisense strand of long dsRNA. The Office alleges that Elbashir teaches 2'-O-methyl and 2'-deoxy modified siRNA duplexes. The Office alleges that Pavco teaches chemical modifications of ribozymes and antisense oligonucleotides, including 2'-O-methyl, phosphorothioates, and inverted deoxy abasic ribose nucleotides. The Office relies on Nyce to allegedly teach targeting CHRM3 with an antisense oligonucleotide.

The Office argues that it would have been obvious to design an siRNA, as taught by Parrish and Elbashir, to target CHRM3 based on the alleged teachings of Nyce, reasoning that one would have been motivated by Hammond, which allegedly teaches that RNAi technology is a more potent methodology than antisense. The Office further argues that it would have been obvious to incorporate 2'-O-methyl or 2'-deoxy modifications as allegedly taught by Nyce and Elbashir, as well as 2'-deoxy-2'fluoro modifications as taught by Parrish and inverted deoxy abasic moieties as allegedly taught by Pavco, into the siRNA duplex allegedly taught by Elbashir or Parrish, reasoning that one would have been motivated because the recited chemical modifications were known in the art to enhance delivery of antisense oligonucleotides or siRNA duplexes. The Office contends that further support is allegedly offered by Caplen, who opines that the problems associated with developing RNAi are the same as those encountered with previous gene therapy approaches. Finally, the Office contends that one would have a reasonable expectation of success that the recited chemical modifications would benefit an siRNA targeted to CHRM3 because each of the modifications were known in the art to benefit antisense oligonucleotides or siRNA duplexes, both of which face the same delivery challenges.

Applicants take the position that there is no *prima facie* case of obviousness for the present claims over Nyce et al., Parrish et al., Elbashir et al., Pavco et al. Hammond et al., and

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<sup>1</sup> Applicant notes that while Parrish may disclose a nucleotide sequence sharing 3 nucleotide homology with CHRM3, that homology level is nowhere near the level of homology recited in the claims under consideration, which recite that an 18 to 27 nucleotide sequence of the antisense strand is complementary to a human CHRM3 RNA sequence comprising SEQ ID NO:305 and the sense strand comprises an 18 to 27 nucleotide sequence of the human CHRM3 RNA sequence.

Caplen *et al.*, because (1) a skilled artisan at the time of the invention would not have found the motivation or reason to modify a double stranded nucleic acid molecule of the claimed size; and (2) even assuming, *arguendo*, that the skilled artisan would have found such a reason, he would not be able to predict which of the millions of potential chemical modification patterns that may be generated from modifying a 18 to 27 nucleotides long constructs using known chemical modifications. Specifically, none of the cited references mention CHRM3 as a potential target for siRNA.

For example, Nyce merely suggests that CHRM3 is a potential target based on antisense oligonucleotide studies; however, it fails to mention or contemplate double-stranded nucleic acid molecules, using these molecules to inhibit CHRM3, or any chemical modifications of double stranded nucleic acid molecules. Therefore, Nyce does not even provide a compelling reason to use double stranded nucleic acid constructs as inhibitors, let alone suggest modifications of these molecules.

The Office argues that a reasonable expectation of success can be found from the cited references because Nyce allegedly suggests that CHRM3 could be a potential therapeutic target. Applicants respectfully but strongly traverse because the Office's contention boils down to a notion that those skilled in the art can find expectation of success based merely on the fact that a gene is known to be associated with certain ailment and thus is an investigation-worthy target.

The knowledge of a worthy target has never been legally sufficient to provide such an expectation. Indeed, such knowledge merely indicates to those skilled in the art a need to investigate the target, but “[r]ecognition of a need does not render obvious the achievement that meets that need.” *Cardiac Pacemakers, Inc. v. St. Jude Medical, Inc.*, 381 F.3d 1371, 1377 (Fed. Cir. 2004). When it comes to modifying what is known in the art, the “mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability” of that specific modification. *See In re Gordon*, 733 F.2d 900, 902 (Fed. Cir. 1984). In other words, the key is the “expectation of success,” and without teaching or suggestion of the specific approaches that should be undertaken to achieve inhibition of that target, there can be no reasonable expectation of success. Otherwise the identification of a target

without more may render all subsequently discovered therapeutic agents (chemical or biological) obvious.

In another example, the teaching of Parrish is limited to dsRNA and therefore does not teach siRNA; nor does it mention or suggest targeting CHRM3. Specifically, Parrish does not teach or suggest the claim limitation that "each strand of said nucleic acid molecule is independently 18 to 27 nucleotides in length," as required by the instant claims because it only teaches chemically modified long (about 742 nts) RNAs. *See Parrish, at page 1081, left column, in the text accompanying Figure 5 ("2-fluorouracil, 2'-aminouracil, 2'-deoxythymidine, and 2'-deoxy-cytidine were incorporated into individual strands of the 742 nt unc-22A segments using T3 and T7 polymerases (Experimental Procedures)" (emphasis added)).* Further, contrary to the Office's allegation, Parrish does not teach any of the chemical modifications of the instantly claimed nucleic acid molecules. Specifically, Parrish fails to teach the claim limitation that "the sense strand includes a terminal cap moiety at the 5'-end, the 3'-end, or both of the 5' and 3' ends of the sense strand" or the claim limitation that "one or more of the nucleotides present in the sense strand and one or more of the nucleotides present in the antisense strand are 2'-O-methyl modified nucleotides". In addition, Parrish fails to teach the claim limitation that "one to ten of the pyrimidine nucleotides present in the sense strand and one to ten of the pyrimidine nucleotides present in the antisense strand are 2'-deoxy-2'-fluoro pyrimidine nucleotides." To the contrary, Parrish describes 2'-deoxy-2'-fluoro uridine modifications but not 2'-deoxy-2'-fluoro cytidine modifications. Indeed, Parrish expressly describes that 2'-deoxy modification of cytidine is not tolerated. *See Parrish, at page 1081, right column ("Modification of cytidine to deoxycytidine ... on either the sense or the antisense strand of the trigger was sufficient to produce a substantial decrease in interference activity.").* Taught by Parrish that cytidines should not be subject to 2'-deoxy modification if interference activity is desired, those skilled in the art would most certainly avoid 2'-deoxy-2'-fluoro cytidine modifications for fear of substantially impaired interference activity. Therefore, Parrish cannot be relied upon for teaching or suggesting the use of 2'-deoxy-2'-fluoro pyrimidine modifications because such modifications encompass both 2'-deoxy-2'-fluoro uridine and 2'-deoxy-2'-fluoro cytidine substitutions. Moreover, Parrish describes 2'-deoxy-2'-fluoro modification of uridine in either

the sense strand or the antisense strand, but **never simultaneously in both strands**, as was first taught by Applicants and as is presently recited in the instant claims. *See, e.g.*, Parrish, at page 1081, left column, Figure 5B (describing that interference activities of unc-22 were retained with a 2'-uracil → 2'-fluorouracil in the sense strand, and unmodified RNA antisense strand; or with an unmodified RNA sense strand and a modified uracil → 2'-fluoro uracil antisense strand). Therefore, Parrish does not provide a reason to use short double-stranded nucleic acid molecules as inhibitors, and does not teach exactly how to modify a short double stranded nucleic acid molecule so as to yield an efficacious siRNA.

In a further example, Hammond et al. merely teach the general mechanism of RNAi and thus fail to contemplate CHRM3 as a target. Further, Hammond does not teach or suggest an siRNA molecule, much less a chemically modified siRNA molecule. In fact, Hammond does not mention chemical modification of any nucleic acid molecules. Hammond teaches only long dsRNA constructs and not short interfering RNA molecules, and accordingly fails to teach or suggest any recited elements of the instantly claimed nucleic acid molecules.

Thus, the Office has not established a compelling reason to make modified dsRNA constructs, let alone the extensively modified constructs of the present claims.

More importantly, however, even assuming that a skilled artisan would find a reason to modify dsRNA constructs with the chemical modifications that were known and used with single stranded nucleic acid molecules such as antisense and ribozyme molecules, potentially hundreds of thousands, if not more, prospective chemical modification patterns may be generated in a double-stranded nucleic acid molecule that is 18 to 27 nucleotides long. The cited references are either silent as to which of the modified molecules might be efficacious, or teach away from making certain of the modifications. Thus, the problem faced by Applicants at the time of this invention did not have a "finite number of identified, predictable solutions," and the instant claims are accordingly not *prima facie* obvious.

In a previous Office Action, and reiterated in the present Office Action, the Office cited Caplen in support of the contention that those skilled in the art would have been motivated to apply chemical modifications known in the ribozyme and antisense art to siRNA duplexes. The Office quoted from Caplen that "[many of the problem associated with developing RNAi as an

effective therapeutic are the same as encountered with previous gene therapy approaches. The key issues of delivering nucleic acids to the required tissue and cell type, while ensuring an appropriate level of efficacy with minimum toxicity induced by the vector system," to support the finding of that motivation. Office Action, mailed July 24, 2006, at page 11 (quoting Caplen, at page 581). Applicants respectfully traverse.

First, contrary to the Examiner's contentions, the Caplen article does not establish that a person skilled in the art at the time of the present invention knew that RNA interference would encounter similar problems as other nucleic acid based therapies and would find motivation in incorporating the same types of modifications. As explained above, this article was published in 2003, after the earliest priority date of the present invention. Moreover, the statements quoted by the Examiner are found in the "Conclusion and expert opinion" section, which ostensibly illustrates the opinion or supposition of the author, who is an acknowledged expert (seeing that the article was published in the journal "Expert Opinion"), and is not indicative of what was known to a person of ordinary skill in the art at the time.

Second, Applicants respectfully submit that the Office has not satisfactorily explained why it would be within the purview of those ordinarily skilled in the art at the time of the present invention to find reasonable expectation of success. In direct contrast with Caplen, which does not inform on the level of knowledge possessed by those of ordinary skill in the art, the Elbashir article cited by the Examiner actually indicates the mindset of those skilled persons at the time, as evidenced by numerous research publications that came soon thereafter. Those publications uniformly suggested that skilled artisans followed the teachings of Elbashir, and designed siRNAs without any modifications other than the 2'-deoxythymidine nucleotides at the 3'-end of the siRNA. *See, e.g.*, Bitko *et al.*, 2001, BMC Microbiology, 1 (34), page 9, left column, "Materials and Methods;" Kuman *et al.*, 2002, Malaria Journal, 1(5), page 9, right column, "Transfection by Inhibitory dsRNA;" and Holen *et al.*, 2002, Nucleic Acid Research, 30, pages 1757-66, Figures 1, 2, and 6. Accordingly, those skilled persons were in fact led down a directly opposite path from the one taken by Applicants.

Countering Applicants' prior arguments that none of the cited references, alone or in combination, make obvious the presently claimed constructs, the Office alleged that "Applicant's interpretation regarding the passage in the Elbashir *et al.* reference is considered erroneous," in

that "Elbashir et al. teach ... modification of 19% of the nucleotides with 2'-deoxy modifications with successful RNAi activity ...[, but] that 100% modification of one or both strands abolished activity. ... Elbshir et al. is silent to any modification percentages between the successful example and the loss of activity at 100% and is silent to any other types of chemical modifications at any percentage." *See* Office Action, at pages 5-6.

Contrary to the Examiner's contentions, Elbashir is by no means silent as to the efficacy of chemical modifications between 19% and 100%. It specifically warns against using more than two 2'-deoxy modified nucleotides at the strands' 3'-ends or having any 2'-O-methyl modifications in "The siRNA user guide," which was cited in the prior response but reiterated here:

2'-deoxy substitution of the 2 nt 3' overhanging ribonucleotides do not affect RNAi, but help to reduce the costs of RNA synthesis and may enhance RNase resistance of siRNA duplexes. **More extensive 2'-deoxy or 2'-O-methyl modifications, reduce the ability of siRNAs to mediate RNAi, probably by interfering with protein association for siRNP assembly.**

Elbashir (EMBO), at page 6885, left column (*emphasis added*). Applicants note that the term "[m]ore extensive" in the second sentence could have only been intended to modify 2'-deoxy" and not the term "2-O-methyl," as the first sentence does not refer to "2-O-methyl" at all and the only experimental data involving 2'-OMe modified siRNA indicated that the corresponding constructs were inactive. Elbashir therefore teaches in no uncertain terms that 2'-O-methyl modifications should be entirely avoided.

Even if Elbashir can be taken as being silent with regard to the efficacy of chemical modifications between 19 and 100%, a contention to which Applicants strongly traverse above, Elbashir's silence does nothing to narrow the hundreds of thousands or more potential types, positions, and/or levels of chemical modifications that may take place in a double-stranded nucleic acid molecule wherein each strand is 18 to 27 nucleotides long. Indeed, as the Examiner has acknowledged, "regardless of the results of these specific modifications at 100% of the positions of one or both strands, Elbashir et al. did modify duplexes and published data regarding **successful inhibition with some duplexes and unsuccessful inhibitions with others.**" Office Action, at page 6. Applicants respectfully submit that, rather than indicating the testing of

known chemical modifications being routine, as the Examiner has concluded, the fact that some of the modified duplexes retain RNAi activity while others do not indicates that those highly skilled in the art, such as the authors of the Elbashir reference, could not predict what specific position(s), levels, or types of chemical modifications amongst hundreds of thousands or more of potential modification patterns would lead to a "successful" RNA duplex.

None of the other cited references serves to narrow down this choice. Not unlike the circumstances of *Takeda*, because of the great number of possible modifications on a 18 to 27 nucleotide long duplex, and because there was no way of predicting which of the modifications might bring about a molecule with RNAi activity, especially in view of the fact that similar modifications did not always yield similar changes in properties, the cited references do not render the instant claims obvious.

For the reasons set forth above, Nyce (WO 99/13886), in view of Parrish *et al.* (Molecular Cell., Vol. 6, pages 1077-1087, 2000), Elbashir *et al.* (The EMBO Journal, Vol. 20, No. 23, pages 6677-6888, 2001), Pavco *et al.* (U.S. 6,346,398 B1), Hammond *et al.* (Nature, 2001, Vol. 2, pages 110-119), Caplen *et al.* (Expert Opin. Biol. Ther., 2003, Jul., 3(4), pages 575-586), alone or in combination, do not render obvious the presently claimed invention. Accordingly, Applicants respectfully request withdrawal of the 35 U.S.C. § 103(a) rejections.

## **Conclusion**

In view of the foregoing remarks, Applicants submit that the claims are in condition for allowance, which is respectfully solicited. If the Examiner believes a teleconference will advance prosecution, she is encouraged to contact the undersigned as indicated below.

Respectfully Submitted,  
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***Hulbert & Berghoff LLP***

Date: October 18, 2007

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